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MICHAEL P. MORRIS
BOEHRINGER INGELHEIM USA CORPORATION
900 RIDGEBURY RD
P O BOX 368
RIDGEFIELD, CT 06877-0368

EXAMINER	
SAMALA, JAGADISHWAR RAO	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
02/08/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

Office Action Summary	Application No.	Applicant(s)	
	10/644,333	DISSE, BERND	
	Examiner	Art Unit	
	JAGADISHWAR R. SAMALA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11-23 and 25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11-23 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicant's Request for Continued Examination and Arguments filed on 11/02/2009.

- Claims 1-8, 10 and 24 have been cancelled.
- Claims 9, 11-23 and 25-32 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/02/2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 11-15, 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Maesen et al (European Respir. J, 8, 1506-1513, 1995) **are withdrawn** in view of Applicant's arguments filed on 11/02/2009.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9, 11-23 and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maesen et al (European Respir. J, 8, 1506-1513, 1995) as applied to claim9, 11-15, 31 and 32 above, and further in view of Skupin (US 5,250,286) and Hochrainer et al (US 6,150,418) **are withdrawn** in view of Applicant's arguments filed on 11/02/2009.

However, upon further consideration a new ground(s) of rejection is made as follow.

Claims 9, 11-15 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerd J Cropp (The American Journal of Medicine, Vol 100, S19-S29, 1996) in view of Peter J. Barnes (Chest, 117(2), 63S-66S, 2000) and Boucher JR (US 2002/0099023).

Applicant claims are drawn to a method for treating an inflammatory component of a disease selected from cystic fibrosis, idiopathic lung fibrosis and fibrosing alveolitis comprising administering, via inhalation a formulation consisting of tiotropium and optionally, physiologically acceptable excipients.

Gerd teaches that braonchodilators such as xanthines, adrenergics, and parasympatholytic have been used for years in the treatment of airway obstruction associated with cystic fibrosis (abstract). Adrenergic and parasympatholytic aerosols such as atropine and ipratropium bromide are more effective for the treatment of airways obstruction associated with cystic fibrosis. Additional disclosure includes that most patients with cystic fibrosis are likely to benefit from bronchodilator therapy when given in adequate doses, appropriate combinations, and by the appropriate route.

Gerd fails to teach a formulation containing tiotropium as active agent for the treatment of cystic fibrobsis, idiopathic lung fibrosis and fibrosing alveolitis.

Peter teaches that tiotropium bromide is a potent, and long-lasting muscarinic antagonist that has been developed for the treatment of COPD (page 63S, see also cited ref. Barnes PJ et al, Tiotropium bromide, a novel long-acting muscarinic antagonist

for the treatment of obstructive airways disease, Life Sci, 1995, 56, 853-859). The tiotropium binds with high affinity to a uniform population of muscarinic receptors in human peripheral lung membranes, and competition studies show that tiotropium is approximately 10-fold more potent than ipratropium and atropine, thus confirming tiotropium as a more potent active agent than ipratropium and atropine (page 64S). Additional disclosure includes that tiotropium is a potent and long-acting anticholinergic agent, where once-daily administration may prove to be more convenient and provide more consistent bronchodilation than the currently recommended three-to four times daily treatment needed for ipratropium (page 66S).

Boucher JR teaches a method for treating chronic obstructive pulmonary disease in a subject. The chronic obstructive pulmonary diseases are characterized by the retention of mucous secretions in the lungs. Examples of such diseases include cystic fibrosis, chronic bronchitis, and primary or secondary ciliary dyskinesia (0004 and 0007). The active compound such as sugar(oligosaccharides), sugar alcohol, organic osmolyte alone or as active compounds used in conjunction with other kind of active agents e.g., bronchodilators may be administered to airway surfaces in an amount effective to increase the volume of fluid on the airway surface(0012). Preferred bronchodilators include ipratropium bromide (0037). Additional disclosure includes that metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquid propellant. The formulation additionally contain one or more co-solvents (ethanol), surfactants, complexing agents such EDTA (0033 and 0040).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporated tiotropium bromide into Gerd's method of treating cystic fibrosis. The person of ordinary skill in the art would have been motivated to make these modifications because Peter teaches that tiotropium bromide binds with high affinity to a uniform population of muscarinic receptors in human peripheral lung membranes, and competition studies show that tiotropium is approximately 10-fold more potent than ipratropium and atropine, and reasonable would have expected success because tiotropium bromide is an antichonergic drug and blocks the muscarinic cholinergic receptor in the smooth muscles of the bronchi in the lungs and is structurally and functionally related to Iprtropium bromide used in Gerd's method for treating cystic fibrosis. Further, both Ipratropium and tiotropium being the muscarinic cholinergic receptors in the smooth muscles of the bronchi in the lungs, opens the bronchi, and would provide relief in chronic obstructive pulmonary disease and cystic fibrosis.

Claims 9, 11-14, 21-23 and 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerd J Cropp (The American Journal of Medicine, Vol 100, S19-S29, 1996) in view of Peter J. Barnes (Chest, 117(2), 63S-66S, 2000) and Freund et al (WO 98/27959, for translation an equivalent US 2001/0008632 is used).

Applicant claims are drawn to a method for treating an inflammatory component of a disease selected from cystic fibrosis, idiopathic lung fibrosis and fibrosing alveolitis comprising administering, via inhalation a formulation consisting of tiotropium and

propellant free inhalable solution, complexing agent optionally, physiologically acceptable excipients.

Gerd teaches that braonchodilators such as xanthines, adrenergics, and parasymptholytic have been used for years in the treatment of airway obstruction associated with cystic fibrosis (abstract). Adrenergic and parasympatholytic aerosols such as atropine and ipratropium bromide are more effective for the treatment of airways obstruction associated with cystic fibrosis. Additional disclosure includes that most patients with cystic fibrosis are likely to benefit from bronchodilator therapy when given in adequate doses, appropriate combinations, and by the appropriate route.

Gerd fails to teach a formulation containing tiotropium as active agent, propellant free-inhalable solution for the treatment of cystic fibrobsis, idiopathic lung fibrosis and fibrosing alveolitis.

Peter teaches that tiotropium bromide is a potent, and long-lasting muscarinic antagonist that has been developed for the treatment of COPD (page 63S). The tiotropium binds with high affinity to a uniform population of muscarinic receptors in human peripheral lung membranes, and competition studies show that tiotropium is approximately 10-fold more potent than ipratropium and atropine, thus confirming tiotropium as a more potent active agent than ipratropium and atropine (page 64S). Additional disclosure includes that tiotropium is a potent and long-acting anticholinergic agent, where once-daily administration may prove to be more convenient and provide more consistent bronchodilation than the currently recommended three-to four times daily treatment needed for ipratropium (page 66S).

Freund teach pharmaceutical preparations in the form of aqueous solutions for the production of propellant-free aerosols for inhalation for the therapy of obstructive lung diseases (abstract). Pharmaceuticals intended for inhalation are dissolved in an aqueous or ethanolic solution or a solvent mixture of ethanol and water (0004).The active anticholinergics includes; ipratropium bromide, oxitropium bromide, tiotropium bromide, budesonide, beclomethasone, disodium cromoglycate, etc. In individual cases, it may be required to add a higher quantity of ethanol or a solution mediator to improve solubility. The solutions are set to a pH of 3.2 to 3.4 with 0.1 or 1 N HCL in 100 ml of finished preparation (0015, 0020, and 0048). Additionally, Freund teaches that addition of an effective amount of a complexing agent, such as, EDTA, citric acid, ascorbic acid and their salts, and more especially disodium salt of ethylenediaminetetraacetic acid (sodium edentate), eradicates the problem of spray anomalies. The effective quantity of complexing agent Na-EDTA is between 10 and 100 mg/100 ml. Also if necessary, ethanol can be added to increase solubility up to 70% by volume. Other adjuvants such as preservatives, especially benzalkonium chloride can be added in amounts of between 8 and 12 mg/100 ml (0009 to 0013).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporated tiotropium bromide into Gerd's method of treating cystic fibrosis. The person of ordinary skill in the art would have been motivated to make these modifications because Peter teaches that tiotropium bromide binds with high affinity to a uniform population of muscarinic receptors in human peripheral lung membranes, and competition studies show that tiotropium is approximately 10-fold more

potent than ipratropium and atropine, and reasonably would have expected success because tiotropium bromide is an antichonergic drug and blocks the muscarinic cholinergic receptors in the smooth muscles of the bronchi in the lungs and is functional equivalent of Iprtropium used in Gerd's method for treating cystic fibrosis. Further, both Ipratropium and tiotropium being the muscarinic cholinergic receptors in the smooth muscles of the bronchi in the lungs, opens the bronchi, and would provide relief in chronic obstructive pulmonary disease and cystic fibrosis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate propellant-free inhalable solution containing complexing agent and benalkonium chloride into Gerd's method for treating cystic fibrosis. The person of ordinary skill in the art would have been motivated to make these modifications because Freund teaches that addition of an effective amount of a complexing agent, such as disodium salt of ethylenediaminetetraacetic acid (sodium edentate), eradicates the problem of spray anomalies, and reasonably would have expected success because it was well known in the art the that aqueous pharmaceutical preparations of propellant-free aerosols for inhalations containing a complexing agent is highly compatible with aerosols, support for the dispersing the active agent and prevent further occurrence of spraying anomalies.

Claims 9, 11-20 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerd J Cropp (The American Journal of Medicine, Vol 100, S19-S29,

1996) in view of Peter J. Barnes (Chest, 117(2), 63S-66S, 2000), Akehurst et al (US 6,919,069).

Applicant claims are drawn to a method for treating an inflammatory component of a disease selected from cystic fibrosis, idiopathic lung fibrosis and fibrosing alveolitis comprising administering, via inhalation a formulation consisting of tiotropium and propellant gas optionally, physiologically acceptable excipients.

Gerd teaches that braonchodilators such as xanthines, adrenergics, and parasymptholytic have been used for years in the treatment of airway obstruction associated with cystic fibrosis (abstract). Adrenergic and parasympatholytic aerosols such as atropine and ipratropium bromide are more effective for the treatment of airways obstruction associated with cystic fibrosis. Additional disclosure includes that most patients with cystic fibrosis are likely to benefit from bronchodilator therapy when given in adequate doses, appropriate combinations, and by the appropriate route.

Gerd fails to teach a formulation containing tiotropium as active agent, propellant gas for the treatment of cystic fibrobsis, idiopathic lung fibrosis and fibrosing alveolitis.

Peter teaches that tiotropium bromide is a potent, and long-lasting muscarinic antagonist that has been developed for the treatment of COPD (page 63S). The tiotropium binds with high affinity to a uniform population of muscarinic receptors in human peripheral lung membranes, and competition studies show that tiotropium is approximately 10-fold more potent than ipratropium and atropine, thus confirming tiotropium as a more potent active agent than ipratropium and atropine (page 64S). Additional disclosure includes that tiotropium is a potent and long-acting anticholinergic

agent, where once-daily administration may prove to be more convenient and provide more consistent bronchodilation than the currently recommended three-to four times daily treatment needed for ipratropium (page 66S).

Akehurst teaches a pharmaceutical aerosol formulation comprising particulate medicament (anticholinergics e.g. ipratropium, atropine or oxitropium col. 2 lines 41-42), 1,1,1,2-tetrafluoroethane (TG134a), 1,1,1,2,3,3,3-heptafluoro-n-propane (TG227) and polar cosolvents such as aliphatic alcohols and polyols (abstract and col. 3 lines 65+). The medicaments of aerosol formulations include anti-allergics, bronchodilators and anti-inflammatory steroids of use in the treatment of respiratory disorders. Additional disclosure includes that pharmaceutical aerosol formulation containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane without recourse to the use of any surfactant resulted in stable formulation having satisfactory dispersions of medicaments.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate propellant gas such as 1,1,1,2-tetrafluoroethane into Gerd's method for treating cystic fibrosis. The person of ordinary skill in the art would have been motivated to make these modifications because Alkehurst teaches that a satisfactory dispersions of medicaments in fluorocarbon or hydrogen-containing chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane can be obtained without recourse to the use of any surfactant in the composition, or the necessity to pre-treat the medicament prior to dispersal in the propellant (col. 2 lines 4-9) and reasonably would have expected success because it was well known in the art the that

hydrocarbons 1,1,1,2-tetrafluorocarbon (TG134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (TG227) are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR R. SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr